Articles in PresS. J Appl Physiol (November 20, 2008). doi:10.1152/japplphysiol.91489.2008

POINT:COUNTERPOINT

EXERCISE-INDUCED INTRAPULMONARY SHUNTING IS *'IMAGINARY'* VS *'REAL'*.

Point: Exercise-Induced Intrapulmonary shunting is imaginary.

By: Susan R. Hopkins, I. Mark Olfert, & Peter D. Wagner

Counterpoint: Exercise-Induced Intrapulmonary shunting is real.

By: Andrew T. Lovering, Marlowe W. Eldridge, & Michael K. Stickland

Point: Exercise-Induced Intrapulmonary shunting is imaginary

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Pulmonary gas exchange efficiency deteriorates with exercise in both in humans and other species, increasing the alveolar-arterial PO2 difference ($AaDO_2$) (2). The potential contributors to this are ventilation-perfusion inequality, alveolar-capillary diffusion limitation and shunt (20). These have been well documented under varying exercise conditions including normoxia, hypoxia and hyperoxia, in particular by the multiple inert gas elimination technique (MIGET) (19). Alveolar, arterial and mixed venous concentrations of inert gases of differing solubility can be measured and used to quantify ventilation-perfusion inequality, alveolar-capillary diffusion limitation (plus any post-pulmonary venous admixture) and intrapulmonary shunt. From this, their individual contributions to $AaDO_2$ can be determined (4, 19), and intrapulmonary shunt has consistently been the least important of the three.

Recently, intrapulmonary shunting, the passage of mixed venous blood through the pulmonary circulation without contact with ventilated regions of the lung (20), has attracted renewed attention as a potential cause of exercising gas exchange impairment (3, 7, 15). This is because of transpulmonary passage of intravenously injected microbubbles demonstrated by agitated saline contrast echocardiography during exercise, but not at rest, (3, 7, 15). The appearance of the microbubbles in the left atrium after 3-5 cardiac cycles is held as evidence of intrapulmonary shunts. Furthermore, it is suggested that these are important determinants of pulmonary gas exchange during exercise (3, 7, 15). Although we do not think transpulmonary bubble transmission is imaginary, we are reminded of the book “Horton Hears A Who” by Theodore Geisel (14). In this children’s classic, Horton the Elephant hears a sound from a speck of dust, which is home to tiny inhabitants known as Whos. The book reinforces the moral that "a person's a person, no matter how small". While it can be argued that a “shunt is a shunt, no matter how small”, several important points should be considered especially when evaluating what microbubble transmission implies for exercising pulmonary gas exchange.

Firstly, the size of transmitted bubbles remains unknown and there are several

assumptions that potentially affect the interpretation of the data, reviewed recently in the context of detecting intracardiac shunting via a patent foramen ovale (21). The technique assumes that most bubbles induced by agitating air in saline are larger than pulmonary capillaries and therefore are trapped by the pulmonary circulation. Although the size of the microbubbles is not uniform, the bubbles that are less than the diameter of a pulmonary capillary during exercise (~10 μ) are argued to degrade to such a small size after transit through the pulmonary circulation that they are no longer detectable (21). This was shown experimentally some 28 years ago using M-mode echocardiography (10), however these experiments have never been repeated using more sensitive modern echo techniques (21). Consequently the size of the bubbles detected in the left heart may be smaller than is assumed, and some bubbles may traverse a normal pulmonary capillary during exercise. In addition, microbubbles are assumed to be rigid, to not deform in the pulmonary circulation, or degrade and then reform with changing gas partial pressures, and that the extent of pulmonary capillary dilation as pulmonary vascular pressures rise during exercise is insufficient to allow passage of bubbles larger than 8-10 μ.

Secondly, agitated saline contrast echocardiography gives only a qualitative assessment of the presence or absence of microbubbles appearing in the left atrium after a specific delay. It cannot quantify blood flow through the responsible vessels. Where flow in these vessels has been quantified using microspheres of 25 and 50 μm diameter, it has either been zero (9), or very small. In Dr. Stickland, Lovering and Eldridge's own data from isolated perfused lungs, such flow averaged 0.01% of cardiac output in baboons, 0.06-0.07% in humans (8) and 0.001-0.05% in dogs. The sole published exception to these observations is in exercising dogs, where microsphere transmission indicated flows <1% of cardiac output (16) in 2 animals and 3.1% in one. Notably in these animals, there was no evidence of gas exchange impairment and PaO_2 was maintained. To explain the average $AaDO_2$ seen during heavy normoxic exercise in man of ~19 Torr (5, 6, 11-13) the shunt would have to be 2.6%, some 37 times greater that than the 0.07% value

indicated above.

Thirdly, the magnitude of the intrapulmonary shunt measured using MIGET in a large number of human subjects during exercise is consistent with the quantitative intrapulmonary shunt data. Although the statement is made that intrapulmonary shunting measured by the MIGET is not observed during exercise in healthy subjects, this is not strictly true. Intrapulmonary shunts are sometimes observed, but they are so small as to be physiologically insignificant. Table 1 shows summarized data from MIGET studies during heavy cycle exercise (90% of $\dot{V}O_2$max) in both normoxia and hypoxia published by our laboratory since 1996 (5, 6, 11-13). In these studies, where $\dot{V}O_2$max ranged from 2000-6000 ml/min, intrapulmonary shunt was always less than 1% of the cardiac output, averaging just 0.2% in normoxia and 0.1% in hypoxia. Importantly, the effect of this level of shunt on gas exchange is minimal, increasing the $AaDO_2$ by less than 2 Torr (Table 1). As a percentage of the total $AaDO_2$, intrapulmonary shunt explains only 7% in normoxia and much less (<1%) in hypoxia.

That intrapulmonary shunt is miniscule is further confirmed by a recent study reporting venous admixture in very fit athletes during exercise breathing pure O2 (18). During 100% oxygen breathing, alveolar PO_2 is elevated to such an extent that ventilation-perfusion inequality and diffusion limitation no longer contribute to the $AaDO_2$ - it can be explained only by right to left shunting (18). In this study (16), venous admixture during 100% oxygen averaged 0.5%, a value also consistent with the previously reported microsphere and inert gas data.

Fourthly, it has never been shown that oxygen exchange across the vessels responsible for microbubble transmission is impaired. It is entirely possible that oxygen exchange is normal, and indeed, as stated above in exercising dogs (14), arterial oxygenation was not impaired, suggesting this to be the case.

Finally has been argued by Drs. Stickland, Lovering and Eldridge that proximal vessel (precapillary) gas inert gas exchange occurring by diffusion may result in an underestimation of intrapulmonary shunt (3, 17) by MIGET. This is because diffusion equilibration of inert gases is much faster than for O_2. However, if that is the case, the problem for O_2 exchange becomes one of diffusion limitation, and not shunt. But even here, there is spectrophotometric evidence (1) that O_2 can also take part in pre-capillary exchange, casting doubt on this explanation.

In summary, flow through vessels responsible for microbubble transmission in exercising humans has never been shown to impair gas exchange, and should not be equated to a shunt, which implies an absence of gas exchange. Furthermore, when intrapulmonary shunts have been quantified, irrespective of technique, they are tiny, like the Whos that Horton the elephant heard, and can account for no more than 1.4 mm Hg, or 7%, of the total $AaDO_2$ of 19 mm Hg. We leave it to the reader to decide if microbubble transmission really implies a shunt, whether a "shunt is a shunt no matter how $_{small}$", and if the effect of intrapulmonary shunt on pulmonary gas exchange is significant.

FIO_2	Normoxia (21%)	Hypoxia (12.5%)
VO_2 (ml/min, STPD)	3685 (728)	2893 (630)
Cardiac Output (l/min)	24.9 (5.1)	24.6 (5.4)
Intrapulmonary Shunt (%)	0.2 (0.7)	0.1 (0.3)
$AaDO_2$ (Torr)	19 (10)	21 (7)
$AaDO_2$ from shunt (Torr)	1.4	0.1
% of $AaDO_2$ from shunt	7.4	0.005

Metabolic and Gas exchange data during very heavy exercise in normoxia (n= 64) and hypoxia (n= 57) from previously published studies (5, 6, 11-13). In all cases the measured intrapulmonary shunt measured by the multiple inert gas technique was less than 1% of cardiac output and had a minimal effect on pulmonary gas exchange.

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Counterpoint: Exercise-induced intrapulmonary shunting is real.

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Funding: AHA Grant-In-Aid 0550176Z (M.W. Eldridge), Canadian Institutes of Health Research New Investigator Award (M.K. Stickland)

The conventional pulmonary circulatory route begins with the pulmonary artery that travels in parallel with the airway, dividing with the airway, until finally reaching the capillary bed within the acinus (4) (Figure 1A). The capillary bed consists of vessels 7 to 10μm in diameter, never exceeding 13μm, even under very high, non-physiologic perfusion pressures(8). The conventional veins then collect blood from capillaries, combining to form progressively larger vessels. Despite this traditional view of the pulmonary vascular circuit, there is substantial anatomic evidence of large-diameter arteriovenous anastomoses in the lung which bypass the traditional blood flow circuit (Figure 1B).

A shunt can be defined as 'a vascular passage by which blood is diverted from its usual or normal path (arteriovenous)(1).' Arteriovenous anastomoses (i.e., shunts) were first described 129 years ago(19) and these pathways allow for arterial blood to bypass the capillary beds and join up with postcapillary venous blood. Large diameter intrapulmonary arteriovenous pathways (or shunts) are known to exist in many species including humans (25; 27), dogs(16), cats(17) and rabbits(17). A critique of previous anatomic work is that the methods used were not physiologic. Recently we have documented intrapulmonary arteriovenous pathways using 50 and 25 μm solid microspheres in healthy human, baboon and dog lungs, which were isolated, ventilated and perfused at physiologic pressures (14; 22). These studies established the patency and functional diameter of some of these intrapulmonary arteriovenous shunt vessels under conditions that more-closely replicate physiologic conditions.

Using all anatomic based approaches, there is a significant amount of evidence that intrapulmonary arteriovenous shunting during exercise is indeed real. In healthy humans we have demonstrated transpulmonary passage of saline contrast bubbles during submaximal through maximal exercise, but not during upright normoxic rest (6; 12; 13; 23; 24). Using saline contrast echocardiography, intrapulmonary shunt is defined as the presence of saline contrast bubbles in the left heart 3 or more cardiac cycles after appearance of contrast bubbles in the right heart (6; 9; 12; 23). Because saline contrast bubbles small enough to travel through even the largest pulmonary capillaries (<13μm) have a life span less than 3 cardiac cycles (even at maximal exercise), transpulmonary passage of these bubbles must occur via large diameter intrapulmonary arteriovenous shunt pathways (2; 15; 18; 28; 29). Of note, saline contrast bubbles can be forced through the normal pulmonary microcirculation using a firmly wedged pulmonary artery catheter with a perfusion pressure of 300 Torr. However, these extreme pulmonary driving pressures do not occur in healthy exercising humans making this an unlikely explanation for the transpulmonary passage of saline contrast bubbles (15).

Consistent with the human, intrapulmonary arteriovenous shunting occurs in dogs. Intravenously injected 25 μm microspheres were found in the tissue and arterial blood of the systemic circulation during exercise but not at rest (22). Dogs were confirmed not to have intracardiac shunts and with an established diameter of 25 μm, these microspheres bypassed the pulmonary capillaries via arteriovenous vessels at least 25 μm in diameter.

Arteriovenous vessels would divert deoxygenated blood away from pulmonary capillaries. If a significant amount of cardiac output was diverted through these pathways when mixed venous partial pressure of oxygen is reduced, such as during exercise, then pulmonary gas exchange as evaluated by the alveolar to arterial oxygen difference ($AaDO_2$) would be impaired. Using the Bergman equation, only a 2% shunt of cardiac output would be required to increase $AaDO_2$ during exercise (11). Indeed, a 1.4 ± 0.8% shunt has been calculated in exercising dogs (22) and exercise-induced intrapulmonary arteriovenous shunting is correlated to $AaDO_2$ in healthy humans (23), suggesting these vessels may play an important role in pulmonary gas exchange impairment during exercise.

Based on the amount of morphological and functional anatomic-based data supporting the existence of inducible intrapulmonary shunts, it may be somewhat surprising that work using the 100% O_2 technique or the multiple inert gas elimination technique (MIGET) has not detected these pathways in healthy humans during exercise(See 5 for complete list of references), suggesting that shunts are imaginary. However, this discrepancy may be explained by precapillary gas exchange and the vasomotor effect of O_2 on the pulmonary circulation, both of which are critically dependent on concentration gradient and physical properties of the gas (Figure 1B & C).

Conhaim and Staub demonstrated precapillary O_2 exchange in rapidly frozen cat lungs(3). In these studies, oxyhemoglobin saturation in 500μm pulmonary arteries from lungs ventilated with room air were as high as 77% at the perimeter of the blood vessel,

while blood at the core of the vessel was as low as 47% saturated with oxygen (3). The size of the perimeter of the blood vessel becoming oxygenated increased from 62μm in normoxia to 401μm in lungs ventilated with 100% O_2. The authors calculated that in normoxia, mixed venous blood may be as much as 15% oxygenated by the time it reaches the alveolar capillary, while blood would be fully oxygenated before reaching the pulmonary capillary when breathing 100% O_2. Importantly, precapillary gas exchange of both O_2 and N_2 have also been demonstrated in humans(10; 20). These studies demonstrated that precapillary O_2 exchange occurs in normoxia, with a greater O_2 exchange occurring in larger vessels with an increased fraction of inspired oxygen. Accordingly, in subjects breathing 100% O_2 during exercise, O_2 exchange would occur proximal to the intrapulmonary arteriovenous pathways(3; 10; 20), and thus these vessels would not be 'seen' as true shunt, as the calculated venous admixture (Qs/Qt) would be minimal (Figure 1C).

Furthermore, a fundamental assumption of the 100% O_2 technique is that the elevated level of inspired oxygen does not have an effect on the pulmonary microcirculation. This does not appear correct, as we have recently demonstrated that exercise-induced intrapulmonary arteriovenous shunting can be eliminated in subjects within two minutes of breathing 100% O_2 (13). These findings raise a concern for the use of the 100% O_2 technique as a valid method for assessing exercise-induced arteriovenous shunt in normoxia, and may explain why venous admixture decreases from 3.5% to 0.5% of cardiac output when subjects breathe 100% O_2 during exercise (26).

With respect to the MIGET, even a small degree of precapillary gas exchange (i.e., restricted to the perimeter blood of a 500 μm vessel) would allow elimination of low-soluble inert gas within the arteries/arterioles. Therefore, if low-solubility gases are exiting the blood within the pulmonary artery upstream of the capillary beds, then these inert gases would never even reach smaller functional arteriovenous shunt vessels (>25 to 50μm), and thus these anatomical shunts would appear imaginary to those using the MIGET. In addition, intrapulmonary arteriovenous pathways themselves may participate in limited gas exchange restricted to their perimeter blood, which would allow some deoxygenated core blood to bypass the pulmonary capillary bed in normoxia, but not be recorded as true mixed venous shunt for the same reasons detailed above (7; 21).

More than 100 years of anatomic data document large diameter arteriovenous pathways in the lung. Recent work has simply demonstrated that these vessels are not always open but become functional under specific conditions, such as during exercise. Is exercise-induced intrapulmonary shunting real? When using anatomic-based techniques (microbubbles and microspheres) they are indeed real.

Figure Legend.

Conventional and alternative views of the pulmonary circulation and gas exchange during exercise. A) Conventional view with the primary gas exchange site restricted to capillary bed; B) Alternative view under normoxic conditions ($P_{A_{O_2}} \approx 120$ Torr), note precapillary O_2 exchange is minimal, but sufficient for the excretion of low solubility MIGET gases while precapillary arteriovenous anastomoses allow for deoxygenated blood to bypass capillary beds and allow for some large diameter bubbles and microspheres to escape entrapment by the capillary bed; C) Alternative view under hyperoxic conditions ($P_{A_{O_2}} \approx$ 700 Torr), note precapillary O_2 exchange is maximal with elimination of MIGET gases while precapillary arteriovenous anastomoses are closed preventing or reducing arteriovenous blood flow and large diameter bubbles and/or microsphere escape.

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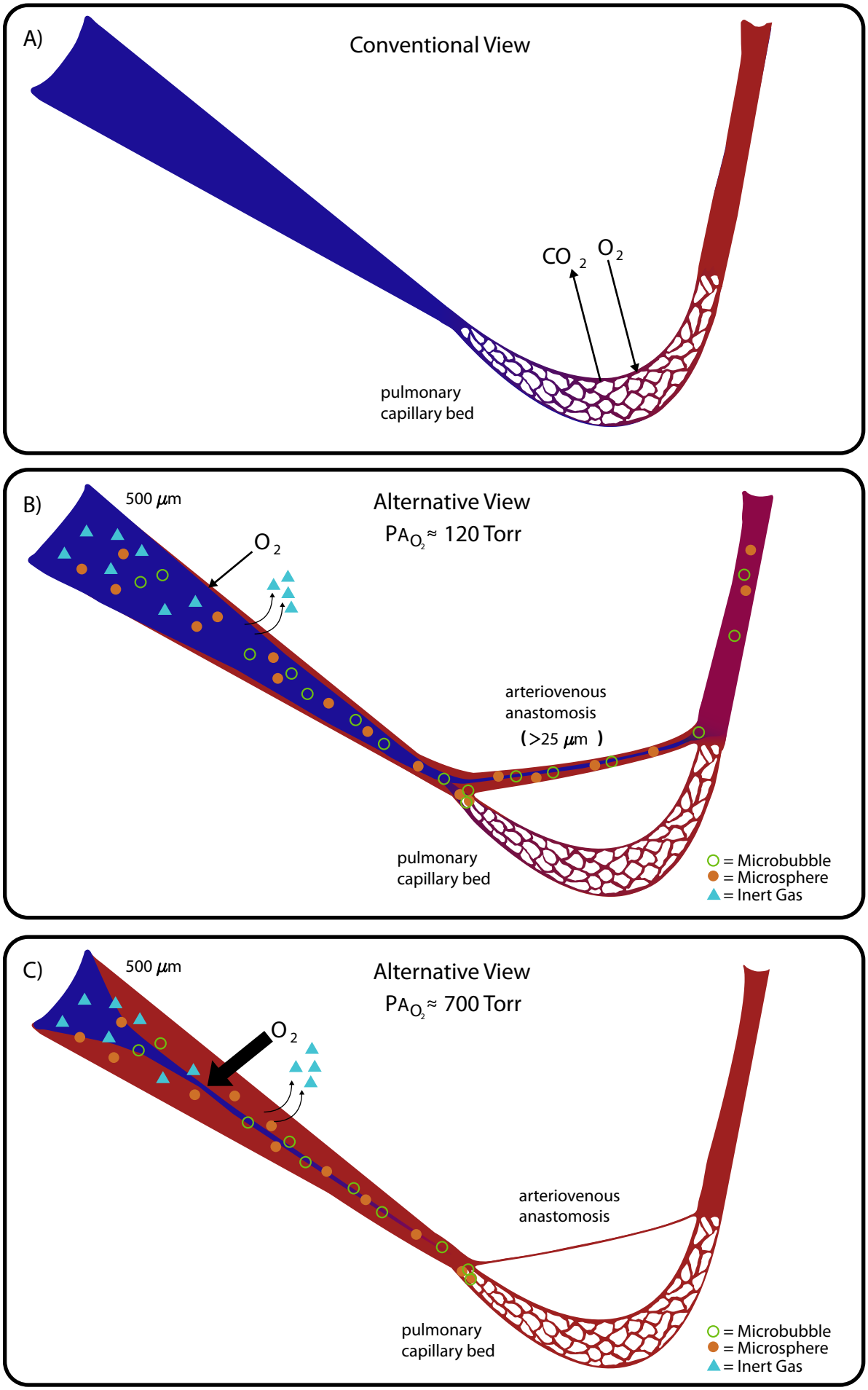

POINT:COUNTERPOINT REBUTTALS

EXERCISE-INDUCED INTRAPULMONARY SHUNTING IS IMAGINARY

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Our colleagues suggest that transpulmonary microbubble passage demonstrates shunting important for gas exchange during exercise (5). However, they themselves show that flow through vessels allowing 25μ microsphere transmission is generally very small and have *never* demonstrated any associated gas exchange effect. They are trying to elevate the status of miniscule arterio-venous pathways into elephant-sized shunts.

They demonstrate microsphere transmission of only 0.001-0.05% of cardiac output at resting flows (6, 8), less than the small ~0.2% found with the multiple inert gas technique (MIGET). During exercise, MIGET-detected shunt in humans (3) and dogs (4) averages 0.1%. In exercising dogs (8), our colleagues report pulmonary microsphere transmission of 1.42%, which they interpret as a 1.42% shunt. In pulmonary gas exchange, shunt has only one definition - blood not exposed to ventilated alveoli during passage through the lungs. Shunted blood doesn't participate in gas exchange and arterial PO_2 thus falls. Importantly in their dogs, PaO_2 *increased* with exercise (from 99 to 106 Torr) while estimated $AaDO_2$ was *unchanged* at 10 Torr. First, PaO_2 increasing to 106 Torr contradicts the assertion that "shunts" are important during exercise. Second, a 10 Torr $AaDO_2$ is entirely accounted for by a shunt of at most 0.6%. Thus, the majority of the 1.42% flow indicated by microspheres cannot be a shunt. Third, if "shunts" appear only during exercise, why didn't the $AaDO_2$ increase during exercise?

Our colleagues find that microbubble transmission correlates with the $AaDO_2$ during exercise (9), but many variables correlate without any cause-and-effect relationship. They also argue that pre-capillary gas exchange impairs the ability of MIGET to detect shunts, as low-solubility gases are eliminated upstream of shunt vessels. However, where pathologic intrapulmonary shunt and hypoxemia are expected (eg., hepatopulmonary syndrome, pulmonary edema), shunt is readily detected with MIGET (1, 7). Also, since pre-capillary gas exchange has been shown for oxygen in normal lungs (2), their explanation is unlikely, as it should similarly overcome "shunting" for O_2 if such

occurred in the arterio-venous pathways found by our colleagues.

Finally, they suggest that using 100% oxygen for measuring shunt is invalid, implying that O_2 constricts some of the pulmonary circulation (5). However what they demonstrate is the disappearance of microbubbles, not of shunt. There are several explanations for this that do not involve rewriting the textbooks on the effects of oxygen on the pulmonary circulation, including how changing gas partial pressures affect microbubble size (10).

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Exercise-induced intrapulmonary shunting is real.

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Funding: AHA Grant-In-Aid 0550176Z (M.W. Eldridge), Canadian Institutes of Health Research New Investigator Award (M.K. Stickland)

Our colleagues present several arguments why intrapulmonary shunts may be imaginary or if real, insignificantly small, like Horton's Whos(4). They suggest that some saline bubbles are small enough to pass through capillaries. However, not all subjects shunt. If bubbles systematically squeezed through capillaries, it would occur in every subject(1; 10). More importantly, in the exercising dog non-deformable 25 μm microspheres traverse the pulmonary circulation during exercise(9). Since capillary distention even under extreme conditions appears limited to <15 μm(2), these microspheres are not squeezing through capillaries.

We agree the shunt flow is small in the isolated lung preparations; however, while the isolated lung studies approximated physiological conditions, they were not equivalent to exercise. This is supported by the observation that a 0.007% shunt is detected in isolated dog lungs but exercising dogs show a shunt of ~2%(9). Interestingly, a 2% shunt accounts for most of the gas exchange dysfunction not measured as V/Q abnormality by MIGET(5). Surprisingly, the authors highlighted work demonstrating no shunting in exercising horses as we have detailed previously the flaws with that study's design(8).

Our colleagues suggest that gas exchange within vessels responsible for microbubble transmission may not be impaired. We would suggest that if subclinical/undetectable pulmonary edema of the ~0.2 μm interstitial space could be responsible for significant O_2

diffusion limitation during exercise, then O_2 diffusion could also be limited (if occurring at all) in a 25-50μm vessel with a wall thickness estimated to be ~2 to 4 μm(7).

Why MIGET is unable to detect these shunts is a mystery. A possible explanation is non-capillary *inert* gas exchange(5). More perplexing, however, is why MIGET has not identified intracardiac right-to-left shunting through a patent foramen ovale (PFO) considering a prevalence of ~25%(3). MIGET would not be able to distinguish between intracardiac and intrapulmonary shunting, however it seems with all the subjects studied a few PFO's would have surfaced, as they have in our studies(1; 6; 10). Recently we have shown that hyperoxia closes inducible intrapulmonary shunt pathways(6) , which would explain why the 100% O_2 test also failed to identify these shunts.

Dr. Seuss said, "Sometimes the questions are complicated and the answers are simple." The evidence of exercise-induced intrapulmonary shunt in simple: saline contrast bubbles and microspheres traverse the pulmonary circulation during exercise, but not at rest. Regardless of their size, like Horton's Whos, the shunts are real, and likely important.

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